MANDAVA ASSOCIATES, LLC

CONSULTANTS IN SCIENCE, TECHNOLOGY AND REGULATORY AFFAIRS
1730 M STREET, N.W., SUITE 906, WASHINGTON, DC 20036-4512
TELEPHONE: (202)-223-1424/1747 • TELEFAX: (202)-223-0141• E-Mail: mandava@compuserve.com

June 25, 2006

201-16359A

Dr. Oscar Hernandez
Director
OPPT Risk Assessment Division
US Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Huntsman-Nissan-TGIC Consortium for HPV Challenge Program for Triglycidyl Isocyanurate (CAS No. 2451-62-9)
Consortium Number for Huntsman-Nissan-TGIC:

Dear Dr. Hernandez:

On behalf of the Consortium for Huntsman-Nissan-TGIC I am pleased to submit our response and modifications to the Test Plan and the Robust Summaries as outlined in your correspondence with EPA's comments on our original to the US EPA HPV Challenge Program for Triglycidyl Isocyanurate (CAS No. 2451-62-9).

This updates submission satisfies the EPA's comments for the TGIC submission. The EPA's comments with the modifications are as follows:

EPA has reviewed this submission and has reached the following conclusions:

1. Substance Identity. The test plan needs to address the issue of isomers that is touched upon in one of the robust summaries.

Response: The test plan on page 5 now addresses this in the Physical – Chemical Paramater Summary and is stated as follows:

Unless otherwise indicated, the toxicology testing described in this Test Plan Summary and in the compilation of Robust Summaries has been conducted using technical grade TGIC. Technical grade TGIC contains two isomers of TGIC, with typical concentrations of the α-isomer ranging from 76 to 80%, and concentrations of the β-isomer ranging from 20 to 24%. The relative amount of the isomers found in technical grade TGIC is apparently not influenced by the method of manufacture. Technical grade TGIC may contain up to 100 ppm of excess epichlorohydrin reactant (oxirane, [chloromethyl], CAS No.106-89-8), as an impurity related to manufacture of the product.

2. Physicochemical Properties. The submitter needs to provide clarifications for boiling point, vapor pressure, and partition coefficient and additional information on melting point.

Responset: We have addressed these issues in the robust summaries on page 12 for boiling point under the Remarks for Methods and the Results Remarks, page 13 for vapor pressure the Vapor Pressure value now reads 7.2, and on page 14 for partition coefficient the value of Log Pow is –0.80.

3. Environmental Fate. The data provided by the submitter are adequate for the purposes of the HPV Challenge Program.

4. Health Effects. The submitted data are adequate for the acute, repeated-dose, and genetic toxicity endpoints; the submitter needs to provide reproductive and developmental toxicity data. Deficiencies in the robust summaries need to be addressed.

Response: The Reproductive and Developmental Toxicity data have been expanded in the Robust summaries on pages 183 to 184 under the Results Remarks and the Results summary for the Toxicology Study includes clinical examinations, Laboratory investigations, Pathology, Analysis of sperm. The Results summary for the fertility study now includes maternal data, Reproductive data in males, Litter data for the hysterectomy subgroup, and the Litter data for the delivery subgroup.

5. Ecological Effects. The submitted data are adequate for all endpoints. The submitter needs to address some missing data elements in the robust summaries.

Response: These have been addressed on under Acute Toxicity to Fish on page 31 (under Measured Concentration and Conclusions). For Acute Toxicity to Aquatic Invertebrates on page 36 (under Methods item # 3 now includes Vehicle control concentration) and on page 37 under Results item # 6 has been added to show immobilization at 100 mg/ml with also modification of the conclusions section indicates that the ECO (24 hr) is 58 mg/L (54.5 mg/L, measured).

EPA COMMENTS ON THE TRIGLYCIDYL ISOCYANURATE CHALLENGE SUBMISSION

Test Plan

Substance Identity

The robust summary for water solubility mentions the existence of the stereoisomers α-TGIC and β-TGIC, but this is not discussed elsewhere in the submission. The test plan needs to describe the isomers, their occurrence in the commercial substance, and whether and how their different physicochemical properties may be relevant to any of the SIDS endpoints (see also melting point and boiling point sections below).

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The melting point and water solubility data provided by the submitter are adequate for the purposes of the HPV Challenge Program.

Melting point. **The submitter needs to include information in the robust summary, similar to that for water solubility, on the stereoisomers α-TGIC (m.p. 105 ^{o} C) and β-TGIC (m.p. 156 ^{o} C)(data from Nordic Expert Group reference), their occurrence in the commercial substance, and their significance for this endpoint, and cite the source of the information. While the summary does not mention decomposition during melting, the boiling point summary states that TGIC decomposes at its melting point; if true, the melting point summary needs to reflect this.**

Boiling point. **The submitter noted in the test plan summary table that adequate data are available for this endpoint. On page 5 of the test plan, the submitter provided a boiling point of 300 ^{o} C (decomposes) for TGIC. However, in the robust summaries, the submitter stated that a boiling point could not be determined because TGIC decomposes at its melting point (95 ^{o} C in the robust summary). The submitter needs to address this discrepancy and provide a correct decomposition temperature. In addition, to the extent that the α- and β-stereoisomers are relevant to the interpretation of this endpoint, such discussion should be added to the summary (see *Melting point*, above).**

***Vapor pressure*.** **The vapor pressure value (0.00072 Pa at 20 ^{o} C or 7.2 x10^{-7} KPa), although adequate, differs from another value of 7.2x10^{-9} KPa (5.4x10^{-8} mm Hg) at 20 ^{o} C (Nordic Expert Group reference). The submitter needs to address the apparent discrepancy.**

Response: Since the commercial product is a mixture of two isomers (α and β) it is not separated. The melting point of the commercial product is 95^{0}C. We have provided information on the commercial product. The commercial product decomposes at >250^{0}C which is below the boiling point and is reflected in the test plan. We have revised the robust summary for melting point and the boiling point to reflect these changes.

The discrepancy for vapor pressure has been addressed with the correct value of 7.2µPA at 20^{O}C as noted on page 13 of the robust summaries under the Vapor Pressure section.

Partition coefficient. **The submitter provided a log Pow of 0.80 at 95 ^{o} C in the robust summaries for TGIC, but in the test plan reports a log Pow of -0.8. The submitter needs to address this discrepancy.**

Response: This discrepancy has been addressed with the correct value of –0.8 as noted on page 14 of the robust summaries under the Partition Coefficient section.

<u>Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)</u>

The data provided by the submitter for these endpoints are adequate for the purposes of the HPV Challenge Program.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

The submitted data are adequate for the acute, repeated-dose, and genetic toxicity endpoints. The submitter needs to address missing study details in the robust summaries.

Response: These have been addressed on under Acute Toxicity to Fish on page 31 (under Measured Concentration and Conclusions). For Acute Toxicity to Aquatic Invertebrates on page 36 (under Methods item # 3 now includes Vehicle control concentration) and on page 37 under Results item # 6 has been added to show immobilization at 100 mg/ml with also modification of the conclusions section indicates that the ECO (24 hr) is 58 mg/L (54.5 mg/L, measured).

***Reproductive/developmental toxicity*. EPA considers the data submitted for the reproductive toxicity endpoint inadequate because the studies only examined males. Although the submitter claims a lack of findings for reproductive effects in the13-week study (page 170), this and other available studies indicate toxicity of TGIC to sperm, spermatids and spermatogonia. In addition, the Test Plan (page 29) reports that lowered weights of ovaries, uterus, prostate, and seminal vesicles were recorded in a 19-day oral study of TGIC. These results underline the need for adequate reproductive toxicity testing.**

No data were presented for studies of developmental toxicity. The discussion presented by the submitter and the available studies are not adequate to address the developmental toxicity endpoint, given the absence of studies on female reproductive toxicity and the observed effects on male reproductive tissues.

The submitter needs to provide data for the reproductive and developmental toxicity endpoints. EPA recommends a combined reproductive and developmental toxicity screening test (OECD TG 421).

Response: The Reproductive and Developmental Toxicity data have been expanded in the Robust summaries on pages 183 to 184 under the Results Remarks and the Results summary for the Toxicology Study includes clinical examinations, Laboratory investigations, Pathology, Analysis of sperm. The Results summary for the fertility study now includes maternal data, Reproductive data in males, Litter data for the hysterectomy subgroup, and the Litter data for the delivery subgroup.

Ecological Effects (fish, invertebrates, and algae)

Adequate data exist for all endpoints; however, the submitter needs to provide the missing study details.

***Invertebrates.* The test plan (pages 6 and 42) incorrectly reports the *Daphnia magna* LC_{50} value as >77 mg/L; according to the robust summary, the EC_{50} value (based on measured concentrations) is 90.6 mg/L.**

Response: The test plan on page 6 now reflects the Robust Summaries page 37 under the section Acute Toxicity to Invertebrates: the EC_{50} value based on measured concentrations is greater than 90.6 mg/ml.

Specific Comments on the Robust Summaries

Generic Comments

In each robust summary, the submitter needs to state the percentage purity of the test substance used in the study.

Response: The robust summaries have been updated to indicate the purity of the test substance used in the study under the heading of purity on all the test pages.

Health Effects

Repeated-dose toxicity. **The robust summary for the 13-week oral toxicity study in male rats (page 154) is missing details including statistical methods and results of statistical analyses, clinical parameters examined and results, a list of tissues and organs examined at necropsy and in histopathology, results of necropsy and histopathology, the number of animals dead or moribund at each dose level, and the number of animals with lowered leukocyte and lymphocyte counts at each dose level.**

Response: The Repeated –dose toxicity (page 154) is now page 163 in the modified robust summary and under item # 3 of the Results and specifically the Results summary for the Toxicology Study includes detailed clinical examinations, Laboratory Investigations, Pathology, Analysis of Sperm. The Results Summary for the Fertility Study includes Maternal Data, Reproductive data in males, Litter data for the hysterectomy and delivery subgroup.

Genetic toxicity (Gene mutations). **The robust summary for the mutagenicity test on ARALDITE PT 810 in the Ames Salmonella/Microsome Reverse Mutation Assay (page 132) is missing details including the criteria for a positive response, individual plate counts, mean number of revertants/plate, and magnitude of increased revertants. This robust summary lists as the AMethod/Guideline Followed@ three FDA and EPA regulations from the Code of Federal Regulations which are Good Laboratory Practice Standards, not test guidelines.**

Response: The robust summary on page 141 (old page 132) has been replaced with OECD 401, represented by Hazelton Protocol #E-401 for the Method/Guideline Followed.

Four robust summaries for mutagenicity tests on Tepic-G in the Ames assay using *Salmonella typhimurium* and *Escherichia coli* are missing details including criteria for a positive response, dose-response information, information on control responses, and details of cytotoxicity.

Genetic toxicity (Chromosomal aberrations). **The robust summary for the A Study to Evaluate the Chromosome Damaging Potential of TK 10622 PT 810 (TGIC 97%) on (page 102) is missing details on the frequency of aberrations at each dose level and on the toxicity of the test material.**

The robust summary for the chromosome analysis in mouse spermatogonial cells following inhalation of TGIC Technical and TGIC 10% Powder (page 99) is missing details on the criteria for a positive response, frequency of aberrations in each test group, and part of the statistical analyses results (Chi-squared Test and One-Way ANOVA). The robust summary reports conflicting results by stating in the results section that the total aberrations achieved statistical significance at $p < 0.01$, and that the genotoxic effect was negative, and in the conclusions section that the response was equivocal in terms of chromosome aberrations. The submitter needs to clarify the results of this study and provide the missing details.

Response: The Chromosomal aberrations study on page 107 (old page 99) now includes details about chromosome aberrations as detailed in the results section which have been divided into the following subcategories: Effects on Mitosis, Results Remarks, Cytotoxic Ratio, and Chromosome Aberrations.

Reproductive toxicity. **For the 13-week oral repeated-dose toxicity study, missing details include a list of reproductive organs examined in necropsy and histopathology, the results of those examinations, and results of observed reproductive toxicity including fertility, gestation, and viability indices.**

Response: The Repeated –dose toxicity on page 163 in the modified robust summary and under item # 3 of the Results and specifically the Results summary for the Toxicology Study includes detailed clinical examinations, Laboratory Investigations, Histopathology, Analysis of Sperm. The Results Summary for the Fertility Study includes Maternal Data, Reproductive data in males, Litter data for the hysterectomy and delivery subgroup.

<u>Ecological Effects</u>

Fish. **The following missing data elements need to be included: fish mortality and/or effects observed at the tested concentration, water hardness, dissolved oxygen content, and pH.**

Invertebrates. **The following missing data elements need to be included: water hardness, dissolved oxygen content, mortality and/or effects seen at each test concentration, and the EC50 value based on measured concentrations.**

Algae. **The following missing data elements need to be included: details on cell density at each test concentration, water hardness, and pH.**

Response: These have been addressed on under Acute Toxicity to Fish on page 31 (under Measured Concentration and Conclusions). For Acute Toxicity to Aquatic Invertebrates on page 36 (under Methods item # 3 now includes Vehicle control concentration) and on page 37 under Results item # 6 has been added to show immobilization at 100 mg/ml with also modification of the conclusions section indicates that the ECO (24 hr) is 58 mg/L (54.5 mg/L, measured).

Conclusions:

Triglycidyl isocyanurate (TGIC) is a trifunctional epoxide resin used primarily as a hardener for polyester-based powder coatings. TGIC is also known by the chemical name: 1,3,5-Triazine-2,4,6(1H,3H,5H)-trione, 1,3,5-tris(oxiranylmethyl)-, identified by Chemical Abstract Service (CAS) No. 2451-62-9.

Based on the information provided, we believe that no further testing is needed on the basis of no risk of adverse effects. We further believe that on the basis of product compositions with TGIC, and low workplace exposure limits the actual risk of any repro effects is quite low. Since the agency relies on exposed populations to make the risk-based argument to perform testing, we believe that no further testing is needed.

In view of the above reasoning, it is our opinion that we have addressed all SIDS Level I endpoints has been adequately addressed for the US EPA HPV challenge program.

The revised table identifies the end points for which robust summaries have been submitted. We believe that no additional testing is needed to satisfy the US EPA HPV Challenge Program for this substance.

Sincerely,

N. Bhushan Mandava, Ph.D.
Consortium for Huntsman-Nissan-TGIC

cc: Mr. Hiromu Ebizuka
Raymond J. Papciak

Enclosures

SUMMARY FOR TGIC TEST PLAN

STUDY	Data Available?	Data Adequate?	Testing Required?
	Y/N	Y/N	Y/N
Physical-Chemical Data			
Melting Point	Y	Y	N
Boiling Point	Y	Y	N
Vapor Pressure	Y	Y	N
Partition Coefficient	Y	Y	N
Water Solubility	Y	Y	N
Environmental Fate & Pathway			
Photodegradation	N	N	N
Stability in Water	Y	Y	N
Transport Between Environ. Compartments (Fugacity)	Y	Y	N
Biodegradation	Y	Y	N
Ecotoxicity			
Acute Toxicity to Fish	Y	Y	N
Acute Toxicity to Aquatic Plants	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	N
Toxicity to Algae	Y	Y	N
Toxicity			
Acute Oral Toxicity	Y	Y	N
Acute Inhalation Toxicity	Y	Y	N
Acute Toxicity to the Eye	Y	Y	N
Acute Dermal Toxicity	Y	Y	N
Genotoxicity *in vivo* (Chrom. Aberrations)	Y	Y	N
Genotoxicity *in vitro* (Gene Mutation)	Y	Y	N
Genotoxicity i*n vitro*	Y	Y	N
Repeated Dose Toxicity	Y	Y	N
Reproductive Toxicity	Y	Y	N
Developmental Toxicity/Teratogenicity	N	Y	N